

IV. Section 112(1) Rejection

The Office Action rejected claims 21-25, 36-37 and 67-80 under 35 U.S.C. section 112, first paragraph, but states that the specification is enabling for claims limited to substance P as the targeting moiety and to a clostridial neurotoxin where the H_C has been removed or modified to reduce its ability to bind to receptors at the neuromuscular junction (page 2 of the Office Action).

All the rejected claims have been amended to so limit the claims. Hence, the rejection should be withdrawn.

V. Section 112(2) Rejection

The Office Action rejected claims 21-25, 36-37 and 67-80 under 35 U.S.C. section 112, second paragraph on various bases (page 7-8 of the Office Action).


All the rejected claims have been amended to remove all of bases for this section 112(2) rejection. Hence, the rejection should be withdrawn.

VI. Conclusion

All issues raised by the Office Action have been addressed. Reexamination, reconsideration and allowance of claims 21-25, 36-37, 67-80 is requested.

Respectfully Submitted,

Date: April 15, 2003


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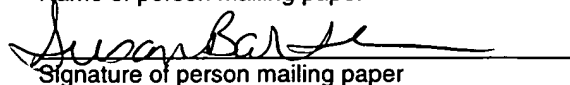
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I hereby certify that this Response to the Office Action and the attached documents referred to as enclosed herein are being deposited with the United States Postal Service on this date April 15, 2003 in an envelope as "Express Mail Post Office to Addressee" Mailing Label number EL385560810US addressed to Commissioner for Patents, Washington DC 20231

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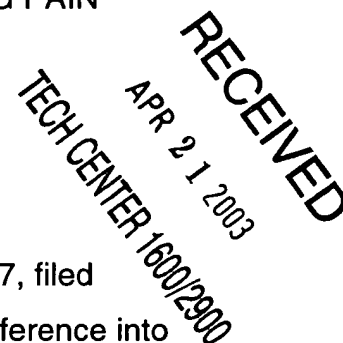
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PAGE ONE OF THE SPECIFICATION

**BOTULINUM CLOSTRIDIAL NEUROTOXIN-SUBSTANCE P CONJUGATE OR
FUSION PROTEIN DERIVATIVES AND METHODS FOR TREATING PAIN**

by

Stephen Donovan



This application is a divisional application of U.S. Serial No. 09/489,667, filed January 19, 2000, the content of which in its entirety is incorporated by reference into the present application.

BACKGROUND

The present invention relates to compositions and methods for treating pain. In particular, the present invention relates to Clostridial toxin derivatives, methods for making the Clostridial toxin derivatives and methods for treating pain using the Clostridial toxin derivatives.

Many, if not most ailments of the body cause pain. The causes of pain can include inflammation, muscle spasm and the onset of a neuropathic event or syndrome. Inflammatory pain can occur when tissue is damaged, as can result from surgery or due to an adverse physical, chemical or thermal event or to infection by a biologic agent. Spasticity or muscle spasm can be a serious complication of trauma to the spinal cord or other disorders that create damage within the spinal cord. Muscle spasm is often accompanied by pain. The pain experienced during a muscle spasm can result from the direct effect of the muscle spasm stimulating mechanosensitive pain receptors or from the indirect effect of the spasm compressing blood vessels and causing ischemia. Since the spasm increases the rate of metabolism in the affected muscle tissue, the relative ischemia becomes greater creating thereby conditions for the release of pain inducing substances. Neuropathic pain is a persistent or chronic pain syndrome that can result from

damage to the nervous system, the peripheral nerves, the dorsal root ganglion or dorsal root, or to the central nervous system.

Neuropathic pain syndromes include allodynia, various neuralgias such as post herpetic neuralgia and trigeminal neuralgia, phantom pain, and complex regional pain syndromes, such as reflex sympathetic dystrophy and causalgia. Causalgia is

THE CLAIMS

1-20. (previously cancelled).

5 21. (currently amended) A method for obtaining an agent for alleviating pain, the method comprising:

(a) producing a genetic construct having nucleic acids ~~codes for encoding~~ a clostridial neurotoxin ~~or component thereof selected from the group consisting of a clostridial neurotoxin, a modified clostridial neurotoxin and~~
 10 ~~fragments thereof;~~

(b) incorporating the construct into a host cell ~~organism;~~

(c) expressing the construct to produce the clostridial neurotoxin ~~component;~~ and

(d) covalently attaching the clostridial neurotoxin to a targeting moiety
 15 which comprises substance P ~~selected from the group consisting of transmission compounds released from neurons in transmitting pain signals and components substantially similar to the transmission compounds, wherein~~
H_C has been removed from the clostridial neurotoxin or modified so as to
reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at
 20 a neuromuscular junction.

22. (original) The method of claim 21, wherein the covalent linkage includes one or more spacer components.

25 23. (currently amended) A method for obtaining an agent for treating pain, the method comprising:

(a) producing a genetic construct having ~~codes for~~ nucleic acids encoding
 (1) a clostridial neurotoxin ~~component selected from a group consisting of~~

~~clostridial neurotoxin, a modified clostridial neurotoxin and fragments thereof~~
and (2) a targeting moiety which comprises substance P ~~selected from the~~
~~group consisting of transmission compounds released from neurons in~~
~~transmitting pain signals and components substantially similar to the~~
transmission compounds;

(b) incorporating the genetic construct into a host cell ~~organism~~; and
(c) expressing the genetic construct to obtain a fusion protein comprising
the clostridial neurotoxin components covalently coupled to the targeting
moiety, wherein H_C has been removed from the clostridial neurotoxin or
modified so as to reduce the ability of the clostridial neurotoxin to bind to a
receptor for the H_C at a neuromuscular junction.

B₁ 24. (original) The method of claim 23, wherein the genetic construct includes genetic
codes that encode for a spacer component between the clostridial neurotoxin
component and the targeting moiety.

25. (original) The method of claim 23, wherein the targeting moiety is substance P.

26-35 (previously cancelled).

36. (currently amended) A plasmid encoding a ~~polypeptide that is derived from a~~
clostridial neurotoxin, comprising:

(a) a first nucleotide sequence region comprising;
(i) a first portion encoding an amino acid sequence region comprising a
targeting moiety that comprises substance P ~~is (1) selected from a~~
~~group consisting of transmission compounds released from neurons in~~
~~transmitting pain signals and components substantially similar to the~~

~~transmission compounds~~, and is (2) able to specifically bind to receptors on cells under physiological conditions; and

(ii) a second portion encoding an amino acid sequence region comprising a translocation element able to facilitate the transfer of a polypeptide across an endosome membrane; and

(b) a second nucleotide sequence region encoding an additional amino acid sequence region comprising a therapeutic element having an intracellular protease biological activity when released into the cytoplasm of a target cell, and an origin of replication directing plasmid replication by a host cell, wherein H_C has been removed from the clostridial neurotoxin or modified so as to reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at a neuromuscular junction.

B₁ 37. (currently amended) A method of making a ~~polypeptide derived from~~ a clostridial neurotoxin comprising:

- (a) inserting the plasmid of claim 36 into a suitable host cell,
- (b) growing the host cell in culture, and
- (c) permitting the host cell to express the polypeptide from the plasmid.

38-66 (previously cancelled).

67. (currently amended) A method for obtaining an agent for alleviating pain, the method comprising:

- (a) producing a genetic construct having nucleic acids encoding ~~codes for~~ a clostridial neurotoxin ~~component~~;
- (b) incorporating the construct into a host cell ~~organism~~;
- (c) expressing the construct to produce the clostridial neurotoxin ~~component~~; and

(d) covalently attaching the clostridial neurotoxin ~~component~~ to substance P, wherein H_C has been removed from the clostridial neurotoxin or modified so as to reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at a neuromuscular junction.

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68. (currently amended) The method of claim 67, further comprising covalently attaching at least one spacer component between the clostridial neurotoxin ~~component~~ and the substance P.

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69. (currently amended) The method of claim 67, wherein the clostridial neurotoxin ~~component~~ is produced by an organism selected from the group consisting of Clostridial beratti, Clostridial butyricum, Clostridial botulinum, and Clostridial tetani.

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B 70. (currently amended) The method of claim 67, wherein the clostridial neurotoxin ~~component~~ is a botulinum toxin selected from the group consisting of serotype A, serotype B, serotype C1, serotype D, serotype E, serotype F, and serotype G.

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71. (currently amended) The method of claim 67, wherein the clostridial neurotoxin ~~component~~ is botulinum toxin serotype A.

72. (currently amended) The method of claim 67, wherein the clostridial neurotoxin ~~component~~ comprises an H_N and an L chain.

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73. (previously added) The method of claim 72, wherein the H_N is produced by an organism selected from the group consisting of Clostridial beratti, Clostridial butyricum, Clostridial botulinum, and Clostridial tetani.

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74. (previously added) The method of claim 72, wherein the L chain is produced by an organism selected from the group consisting of Clostridial beratti, Clostridial butyricum, Clostridial botulinum, and Clostridial tetani.

75. (previously added) The method of claim 72, wherein the H_N is obtained from a botulinum toxin selected from the group consisting of botulinum toxin serotype A, serotype B, serotype C1, serotype D, serotype E, serotype F, and serotype G.

76. (currently amended) A method for obtaining an agent for alleviating pain, the method comprising:

- B₁
- (a) producing a genetic construct having nucleic acids ~~codes for encoding~~ a botulinum toxin;
 - (b) incorporating the construct into a host cell ~~organism~~;
 - (c) expressing the construct to produce the botulinum toxin; and
 - (d) covalently attaching the botulinum toxin to substance P.

77. (currently amended) A method for obtaining an agent for alleviating pain, the method comprising:

- (a) producing a genetic construct having nucleic acids encoding ~~codes for~~ a botulinum toxin serotype A;
- (b) incorporating the construct into a host cell ~~organism~~;
- (c) expressing the construct to produce the botulinum toxin serotype A; and
- (d) covalently attaching the botulinum toxin serotype A to substance P, wherein H_C has been removed from the botulinum toxin or modified so as to reduce the ability of the botulinum toxin to bind to a receptor for the H_C at a neuromuscular junction.

78. (currently amended) A method for obtaining an agent for alleviating pain, the method comprising:

- 5 (a) producing a genetic construct having nucleic acids encoding ~~codes for~~ a botulinum toxin, wherein the portion encoding an Hc of the toxin has been removed;
- (b) incorporating the construct into a host cell ~~organism~~;
- (c) expressing the construct to produce the botulinum toxin; and
- (d) covalently attaching the botulinum toxin to substance P.

10 79. (currently amended) A method for obtaining an agent for treating pain, the method comprising:

- B₁ (a) producing a genetic construct having nucleic acids encoding ~~codes for~~ (1) a clostridial neurotoxin ~~component~~ and (2) substance P;
- (b) incorporating the genetic construct into a host cell ~~organism~~; and
- 15 (c) expressing the genetic construct to obtain a fusion protein comprising the clostridial neurotoxin ~~component~~ covalently coupled to the substance P, wherein H_C has been removed from the clostridial neurotoxin or modified so as to reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at a neuromuscular junction.

20 80. (currently amended) The method of claim 79, wherein the genetic construct includes genetic codes that encode for a spacer component between the clostridial neurotoxin ~~component~~ and substance P.
